*Short Communication*

# Effects of intranasal oxytocin on the attentional bias to emotional stimuli in patients with bulimia nervosa

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Number of words (minus abstract and references): 1,986
Number of references: 24

Highlights for review

- Dysregulated social perception is a possible causative factor for interpersonal difficulties in BN
- Oxytocin inhibits the amygdala response to threat and modulates emotional reactivity
- BN shows a similar increase in attentional processes to anger as the healthy comparison group
- Intranasal oxytocin reduced the attentional bias to anger in both BN and the healthy comparison group

**Abstract**

*Background*: Bulimia nervosa (BN) is characterized by binge eating and emotional dysregulation including increased negative affectivity (anger, anxiety). The aim of this study was to examine the effect of oxytocin on attentional processes towards anger in patients with BN.

*Method*: The study design consisted of a double-blind, placebo-controlled within-subject crossover, single dose experiment. Sixty-four women (31 patients with BN and 33 healthy comparisons) completed self-reported measures to evaluate emotional difficulties and were administered a single dose of intranasal oxytocin (40IU) or placebo followed by a visual probe detection task to examine attentional orienting to angry or happy faces.

*Results*: Patients with BN reported higher emotional dysregulation and more difficulties in controlling anger compared to the healthy comparison group. Patients with BN and the healthy women exhibited similar attentional bias to angry faces in the placebo condition. Intranasal oxytocin reduced the attentional bias towards angry faces in both the BN patients and the healthy women.

*Conclusions*: We found that a single dose of oxytocin reduced vigilance towards angry faces in patients with BN as well as healthy women. The results showed that patients with BN are not different from healthy women in terms of vigilance towards threat.

**Keyword:** oxytocin, bulimia nervosa, anger, emotional regulation, attentional bias

## 1. Introduction

A recent maintenance model of bulimia nervosa (BN) has proposed that elevated impulsivity, sensitivity to punishment, and interpersonal difficulties reduce the rewarding aspects of social interaction (Treasure et al., 2018). This in turn is believed to feed into increased emotion dysregulation, shame, and information processing biases, leading to greater reliance on eating as a coping mechanism and source of reward. The model is supported by findings that people with BN show increased attention and sensitivity towards negative social cues (Caglar-Nazali et al., 2014; Cardi et al., 2014; Cardi et al., 2013). Observational studies have also reported that binge eating episodes are frequently preceded by negative affect, especially anger and interpersonal distress (Haedt-Matt and Keel, 2011). Moreover, experimental studies have found that people with BN are characterized by a high propensity to express anger inadequately (Krug et al., 2008), which can lead to binge eating through impulsive emotional dysregulation (Amianto et al., 2012). Furthermore the trajectory of improvement in emotional regulation associated with treatment varies between eating disorders with the most change found in BN (Mallorqui-Bague et al., 2018).

Oxytocin, a neuropeptide, has a central role in neural circuits involved in social behaviour, appetite, anxiety, and stress. Previous work has suggested that oxytocin plays an important role in regulating social cognition by altering amygdala and prefrontal reactivity to social cues (Guastella and MacLeod, 2012; Ross and Young, 2009). Improvements in emotion recognition and theory of mind, and increased attention towards positive social cues following intranasal oxytocin among healthy people (Bakermans-Kranenburg and van, 2013; Domes et al., 2013; Macdonald and Macdonald, 2010). Oxytocin might contribute to the etiology of eating disorders, and social cognition is one of these pathways (Giel et al., 2018). Our pilot study found intranasal oxytocin similarly improved emotion recognition sensitivity in BN and healthy people (Kim et al., 2015), which suggested that reactivity to emotional stimuli may be a greater source of difficulties in BN and therefore, examining the effects of oxytocin in this area would be of interest.

The aim of the study was to build on existing literature and examine the impact of a single dose of intranasal oxytocin on attentional bias towards emotional cues in BN. As anger in particular is believed to play an important role in the maintenance of disordered eating in BN, we were interested

in examining the impact of intranasal oxytocin on attentional reactivity to angry in addition to happy and neutral faces. Our first hypothesis was that patients with BN would show increased attention to angry faces due to sensitivity towards negative social cues. Our second hypothesis was that oxytocin would reduce attentional bias towards anger and increase the bias towards positive and neutral faces in BN.

## 2. Materials and methods

### 2.1. Participants

Sixty-four young women [31 patients with BN and 33 healthy comparisons (HC)] took part in this study. Patients with BN were recruited from the outpatient clinic of Eating Disorders Clinic at Seoul Paik Hospital, Seoul, South Korea. The BN diagnosis was confirmed using a Structured Clinical Interview (First et al., 2007) based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). The exclusion criteria for patients were as follows: active substance use disorder and psychotic disorder. Those who had other comorbidities were allowed. In the sample, the common psychiatric comorbid disorders were depressive disorders (n=13), anxiety disorders (n=8) and borderline personality disorder (n=7) based on DSM-5. Other than the 7 patients who were taking fluoxetine, patients who were taking psychiatric medications were excluded.

The HC participants were students from the women's university in Seoul, South Korea. The inclusion criteria were healthy females without a history of medical or psychiatric illnesses, not taking regular medication including the contraceptive pill, and a minimum age of 17 years. The exclusion criteria were as follows: self-reported history of psychiatric, developmental, or neurological disorders, and substance dependence.

The sample size was based on an a priori power analysis conducted with G*Power (Faul et al., 2007), which indicated a minimum sample size of 60 (power = 0.8) to detect significant effects. All participants provided written informed consent prior to participating in the study. The study protocol was approved by both the Korean Food and Drug Association Institutional Review Board (approval number: 12061) and the Institutional Review Board of Seoul Paik Hospital (approval number: IIT-

2012-096). This study was registered with the Clinical Research Information Service (http://cris.nih.go.kr) (registration number: KCT0000716).

2.2. Experimental design

We applied a double-blind, placebo-controlled, within subjects, crossover design. The preparation methods for the oxytocin and placebo are shown in Supplementary Information 1. Participants without amenorrhea (n = 61) were tested during the follicular phase of their menstrual cycle (approximately days 3 through 12). All participants received a single dose of both oxytocin (40 IU per dose) and placebo in separate sessions in accordance with current guidelines (Carson et al., 2013). Each participant visited the laboratory twice for testing: once for the placebo condition and once for the oxytocin condition. The order of the placebo or oxytocin administration for each participant was determined randomly by a project coordinator who was not involved in the experiment. The visual probe detection task commenced 45 minutes after the intranasal administration of oxytocin or placebo. For further details please see Supplementary Information 2.

2.3. Measurements

2.3.1. Self-reported psychometric assessments

All participants completed self-reported measures to evaluate emotional difficulties and eating disorders psychopathology. For further details please see Supplementary Information 3.

2.3.2. Visual probe detection task

A visual probe detection task was used to measure attentional biases. The stimuli consisted of happy (n = 15), angry (n = 15), and neutral (n = 15) facial expressions of 15 adults were selected from 2 databases of Korean facial expressions of emotion (Lee et al., 2013; Park et al., 2011). An emotional and a neutral face were presented simultaneously, side by side on a screen followed by a probe either at the target's location (emotional face) or at the distractor's location (neutral face). A fixation cross was displayed at the centre of the screen for 750 ms followed by the target and non-target stimuli pair for 1,000 ms. The reaction time (RT) was measured from the onset of the visual

probe following the prime until the button press. For further details please see Supplementary Information 4.

2.4. Statistical analysis

We followed a standard analytical procedure for the visual probe detection task (Bradley et al., 1999). Only RTs from trials in which probes were correctly identified were included in the analysis. The correct response rates were 99.9% for the BN group and 99.7% for the HC group. Mean RTs were calculated for each participant, and the outlier trials were removed by excluding detection latencies beyond two standard deviations from their mean (i.e., from each individual's mean RTs across all stimuli).

Attentional bias (AB) was calculated for each matched trial type (happy-neutral, angry-neutral) by subtracting the mean RT for probes replacing the emotional prime from the mean RT for probes replacing the neutral prime. A positive AB indicated increased attention for the emotional prime while a negative AB indicated attention away from the emotional prime. The AB data were analyzed by a 2x2x2 mixed linear model using SPSS 23 (SPSS Inc., Chicago, IL, USA). The drugs (oxytocin and placebo), emotions (happy and angry), and groups (BN and HC) were entered as fixed effects while the subjects were the random effect. Multiple models were built to evaluate the model fit based on variance-covariance structures. Based on the results from the 2 Log Likelihood, the Akaike Information Criterion, and the Schwarz Bayesian Criterion, final models with a diagonal structure were reported (Littell et al., 2000). The significant interactions were post hoc tested with simple effects tests, and the effect sizes for independent and dependent t-tests are reported using Cohen's *d*. Statistical significance was set at $p < 0.05$.

## 3. Results

3.1. Demographic and clinical characteristics

Demographic and clinical characteristics of the participants are summarized in Table 1. Ages, body mass indexes (BMI, $kg/m^2$), and IQ levels were not significantly different among the patients with BN and the HC participants.

(Table 1. Clinical characteristics of patients with bulimia nervosa and the healthy comparisons)

3.2. Attentional bias to anger/happy expression faces

The AB scores among the BN and HC groups following oxytocin and placebo administration are presented in Table 2. The mixed model revealed no effects from the Drug x Emotion x Group interaction [$F(1,228.082) = 0.002$, $p = 0.965$] or Emotion [$F(1,228.082) = 0.136$, $p = 0.712$] on the AB scores. However, there were effects from the Drug x Emotion interactions [$F(1,228.082) = 6.413$, $p = 0.012$] and Drug [$F(1,228.082) = 6.118$, $p = 0.014$] on the AB scores. Oxytocin significantly reduced the AB towards angry faces in both the patients with BN and HC participants. A simple effect test showed that the AB to angry faces was reduced by oxytocin [$F(1,120.632) = 10.217$, $p = 0.002$] whereas the AB to happy faces was not [$F(1,118.034) = 0.002$, $p = 0.962$]. Figure S1 for AB scores is presented in Supplementary Information 5. In addition, we explored whether oxytocin induced changes in the AB scores correlated with psychometric variables or not. The results are shown in Supplementary Information 6 and 7, and further investigation was not carried out as there were no differences in AB between the BN and HC groups.

(Table 2. Attentional bias scores (in ms) towards angry and happy faces in the visual probe task for the oxytocin or placebo sessions in patients with bulimia nervosa and the healthy comparisons)

**4. Discussion**

The aim of this study was to examine the effect of intranasal oxytocin on the attentional reactivity to anger in patients with BN. The findings revealed that relative to the HC group, the BN participants did not show greater AB towards anger in the placebo condition. Instead, both groups showed similar vigilance towards the angry faces, which was attenuated by intranasal oxytocin.

The present findings are supported by previous findings reporting positive impact of intranasal oxytocin on social cognition and cooperation among healthy individuals (Bakermans-Kranenburg and

van, 2013; Domes et al., 2013; Macdonald and Macdonald, 2010). Moreover, findings from our previous work also showed that oxytocin similarly improved sensitivity to recognize basic emotions among the BN and HC participants (Kim et al., 2015). Therefore, taken together these findings suggest that intranasal oxytocin may have a generally positive impact on social-emotional processing.

In the context of the maintenance model of BN (Treasure et al., 2018), the present findings are encouraging that intranasal oxytocin could help to reduce elevated sensitivity to negative social cues, which in turn could help to alleviate information processing biases. Thus, ultimately intranasal oxytocin could potentially help to break the loop in BN. However, it is of importance to note that the present study did not find a group difference in AB towards anger or on the effects of oxytocin on AB. Thus, research with larger sample size may be needed to explore this possibility further.

In this study, taking fluoxetine was accepted as an inclusion criterion. Although, it is a common clinical practice for treating BN, it might be confounding the effect of oxytocin on AB as SSRIs may modify specific neural dysfunctions correlated to negative cognitive biases (Di Simplicio et al., 2012). Therefore, the effect of fluoxetine on oxytocin and AB needs to be investigated in a further study.

The main limitation of the present study was the relatively small sample size, which prevented further exploration of the potential confounding effects of individual differences, including childhood trauma and comorbid diagnoses. Additionally, a recent meta-analysis reported that the visual probe task may not be optimal for measuring AB and recommended that future studies should opt for more sensitive measures to examine the effects of oxytocin in AB (Leppanen et al., 2018). Third, the comorbid psychiatric disorders might influence the effect of oxytocin and AB. Finally, as the study was carried with a Korean sample, the study needs to be replicated for other racial ethnic populations to determine the generalizability of the findings.

In conclusion, patients with BN show similar increased attention to threat stimuli, and similar moderation effects with oxytocin as found in healthy comparison group.

**Role of funding sources**

This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (2016R1D1A1A09917877). They had no role in the design, data collection, analysis, interpretation, or writing of this report. The corresponding author has full access to all of the data in this study and has final responsibility for the decision to submit for publication.

**Author contributions**

YK and JT were involved with the study design. YK conducted the data collection and JE conducted the data analysis. YK, JT, JL, and ML were involved with the interpretation of results and the preparation of the draft article. All authors read and gave their approval of the final version of the article.

**Conflicts of interests**

There are no conflicts of interest for all authors.

**Acknowledgements**

We thank Ji Won Kang for her help collecting the data and Yo-Han Jeon for his help for the oxytocin analysis.

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304 **Table 1.** Clinical characteristics of patients with bulimia nervosa and the healthy comparisons

| Characteristics | BN (N=31) | HC (N=33) | *t* | *p* | *d* |
|---|---|---|---|---|---|
| Age, years | 23.87(3.99) | 22.45(2.22) | 1.76 | 0.082 | 0.42 |
| Age of onset, years | 19.90(4.72) | NA | NA | NA | NA |
| BMI, kg/m$^2$ | 20.79(2.62) | 20.85(2.40) | -0.08 | 0.932 | 0.02 |
| Intelligence | 106.44(13.79) | 111.20(6.28) | -1.69 | 0.096 | 0.44 |
| EDE-Q | | | | | |
| Restraint | 2.1(1.76) | 0.87(0.86) | 3.53 | 0.001 | 0.89 |
| Eating Concern | 2.77(1.67) | 0.60(0.77) | 6.56 | <0.001 | 1.68 |
| Shape Concern | 3.50(1.58) | 1.68(1.11) | 5.25 | <0.001 | 1.34 |
| Weight Concern | 4.04(1.46) | 2.44(1.20) | 4.72 | <0.001 | 1.20 |
| Global | 3.11(1.36) | 1.40(0.85) | 5.93 | <0.001 | 1.51 |
| BDI | 18.52(12.23) | 7.58(7.00) | 4.31 | <0.001 | 1.09 |
| STAI | | | | | |
| State | 53.65(13.16) | 43.03(11.52) | 3.37 | 0.001 | 0.85 |
| Trait | 57.81(12.32) | 44.03(11.32) | 4.58 | <0.001 | 1.16 |
| STAXI | | | | | |
| Anger_State | 13.55(7.97) | 11.79(4.99) | 1.06 | 0.290 | 0.26 |
| Anger_Trait | 22.06(7.26) | 18.73(6.13) | 1.99 | 0.051 | 0.49 |
| Anger_Supression | 19.81(4.85) | 17.79(4.27) | 1.77 | 0.082 | 0.44 |
| Anger_Expression | 17.32(4.43) | 15.03(3.95) | 2.18 | 0.032 | 0.54 |
| Anger_Control | 19.35(5.35) | 19.24(4.92) | 0.08 | 0.930 | 0.02 |
| DERS | | | | | |
| Non-acceptance | 16.42(6.18) | 9.82(5.64) | 4.46 | <0.001 | 1.11 |
| Goals | 17.03(3.71) | 13.90(2.91) | 3.69 | <0.001 | 0.93 |
| Impulsivity | 15.74(5.20) | 11.85(5.07) | 3.03 | 0.004 | 0.75 |
| Awareness | 17.65(4.90) | 19.68(3.92) | -1.80 | 0.076 | 0.45 |
| Strategies | 21.68(6.34) | 15.16(5.69) | 4.25 | <0.001 | 1.08 |
| Clarity | 12.65(2.60) | 12.97(1.74) | -0.57 | 0.568 | 0.14 |

Data are shown as mean (SD). d = Cohen's d, BN = bulimia nervosa, HC = healthy comparison, BMI = body mass index, EDE-Q = Eating Disorders Examination Questionnaire, BDI = Beck Depression Inventory; STAI-State, Spielberger State and Trait Anxiety Inventory State Score, STAI-Trait = Spielberger State and Trait Anxiety Inventory Trait score, STAXI = State and the Trait Anger Expression Inventory, DERS = Difficulties in Emotion Regulation Scale, Non-acceptance = non-acceptance of emotional responses, Goal = difficulties engaging in goal-directed behaviour, Impulsivity = impulse control difficulties, Awareness = lack of emotional awareness, Strategies = limited access to emotion regulation strategies, Clarity = lack of emotional clarity, NA = Not applicable

305 **Table 2.** Attentional bias scores (in ms) towards angry and happy faces in the visual probe detection task for the
306 oxytocin or placebo sessions in patients with bulimia nervosa and the healthy comparisons

| Prime face | BN (n=31) | | *t*(*df*=30) | *p* | *d* | HC (n=33) | | *t*(*df*=32) | *p* | *d* |
|---|---|---|---|---|---|---|---|---|---|---|
| | Placebo | Oxytocin | | | | Placebo | Oxytocin | | | |
| Happy | 10.68(79.96) | 9.72(74.34) | 0.04 | 0.967 | 0.01 | 11.55(71.99) | 13.72(58.35) | -0.14 | 0.889 | -0.03 |
| Angry | 40.44(95.34) | -12.10(90.34) | 2.67 | 0.012 | 0.47 | 39.76(101.35) | -9.51(74.97) | 2.17 | 0.037 | 0.37 |

Data are shown as mean (SD). Analyzed by paired t-test. BN = bulimia nervosa, HC = healthy comparison, *d* = Cohen's *d*.

**List of Supplementary Information**

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**Supplementary Information 1**

**Preparation of oxytocin and placebo**

Intranasal oxytocin sprays were formulated by JW Pharmaceuticals (Seoul, South Korea) from oxytocin powder (Hemmo Pharmaceuticals, Mumbai, India). First, 35.2 mg of oxytocin (568 U) were mixed into 300 mL of 0.9% sodium chloride solution for which the pH was adjusted to 4.01 with 10× diluted acetic acid. The placebo spray (pH 4.01) was also formulated with 0.9% sodium chloride solution and acetic acid, but without the peptide. The filtered and sterilized solutions were sealed in 1.5 mL vials and frozen. On the day of use, the vials were thawed and kept in a refrigerator (4°C) until required. A clinician prepared the nasal spray by transferring oxytocin or the placebo from the vial into a nebulizer. The nebulizer was primed and given to the participants to self-administer the nasal spray while being monitored by a clinician.

**Supplementary Information 2**

**Study flow**

The participants were tested in a private room at Seoul Paik Hospital. The experiments were carried out at 1430h, and the participants were instructed to eat lunch 2 hours before drug administration and to refrain from further eating and drinking (other than water). Alcohol and caffeine were prohibited on the day of the drug administration. Upon arrival, the participants completed baseline measurements for physical symptoms, including abdominal, neurological, dermatological, and cardiac. They were then asked to self-spray the full 1.5 mL dose of oxytocin or the placebo nebulizer into their two nostrils under the supervision of a clinician. Each oxytocin spray delivered 40 IU of oxytocin, an amount determined based on a recent review, which reported that short-term use of intranasal oxytocin of up to 40 IU (per dose) in male and female humans resulted in no detectable subjective changes in a controlled research setting (MacDonald et al., 2011). Each inhalation of the test solution into a single nostril contained approximately 4 IU of oxytocin. Subsequently, the participants received oxytocin or placebo in ten puffs delivered to alternating nostrils at 30 s intervals. Neither the participant nor the clinician was informed of the drug assignment on the day.

After intranasal administration of oxytocin or placebo, the participants completed self-reported measurements to assess their psychological states. This was followed by the dot-probe task, which began 45 minutes after the administration of the drug. At the end of the day, each participant carefully completed follow-up measurements for adverse physical symptoms. The second appointment was then scheduled for 1 week after the first appointment.

**Supplementary Information 3**

**Self-reported psychometric assessments**

1. Eating Disorder Examination – Questionnaire (Fairburn and Beglin, 1994)

The EDE-Q assesses the main behavioral features of an eating disorder over the past 28 days based on a self-report. The questionnaire consists of 36 items on a 7-point forced choice rating scale that measures weight, shape, eating related concerns, and dietary restrictions. The Korean EDE-Q is a reliable and valid instrument, and the Cronbach's alpha of the Korean EDE-Q is 0.93 for the global scale and 0.79~0.92 for the 4 subscales (Lim et al., 2010).

2. State-Trait Anger Expression Inventory (STAXI) (Spielberger, 1991)

The STAXI is a 44-item, self-report questionnaire that evaluates different facets of anger on a five-point scale: State Anger (the intensity of feeling angry, 10 items), Trait Anger (disposition toward anger, 10 items), Anger-in (proneness to suppressing anger, 8 items), Anger-out (tendency to express anger towards other people and objects, 8 items), and Anger Control (tendency to control the expression of anger, 8 items). Items are rated using 4-point Likert responses. The STAXI has been validated for various normal and clinical populations and has good psychometric properties (the internal consistency of the STAXI-2 scales and subscales ranging from 0.73 to 0.95). The Korean adaptation of STAXI (STAXI-K) (Chon, 1996) has the same factor structure as the original STAXI, although four items were replaced with newly constructed items. STAXI-K has a good internal consistency with a Cronbach's alpha of over 0.70, except for Anger-in for female participants (0.69). The test-retest reliability coefficient of the STAXI-K over a 3-week period was also stable.

3. Difficulties in Emotional Regulation Scale (DERS) (Gratz and Roemer, 2004).

DERS is a 36-item self-report scale measuring emotional regulation. The participant is asked to rate responses across a five-point scale: 1=almost never (0–10%), 2=sometimes (11–35%), 3=about half the time (36–65%), 4=most of the time (66–90%) and 5=almost always (91–100%). There are six discrete, but interconnected subscales and a total score. Higher scores indicate greater difficulties with regulating emotions. The six subscales are as follows: (1) Non-acceptance of emotional responses, which is a tendency to have negative secondary responses to one's own negative emotions or not accepting emotional reactions to distress; (2) Difficulties in engaging in goal-directed behavior, which involve difficulties concentrating and accomplishing tasks when experiencing negative emotions; (3) Impulse control difficulties, which are difficulties with remaining in control of behavior when experiencing negative emotions; (4) Lack of emotional awareness, which are difficulties associated with attending to and acknowledging emotions; (5) Limited access to emotion regulation strategies, which is a belief that, once upset, little can be done to regulate emotions, and (6) Lack of emotion clarity, which is how much an individual knows and understands the emotions they are experiencing. We used the Korean DERS (Cho, 2007), in which the Cronbach's α for the total score was 0.92, comparable to Gratz and Roemer's (2004) score of 0.93. Like Gratz & Roemer, Cronbach's α values for the subscales of the Korean version were in the range of 0.76~0.89.

4. Other measurements

Depression and anxiety levels were assessed for each subject using the standardized Korean versions of the Beck Depression Inventory (BDI) (Beck et al., 1961) and the Spielberger State and Trait Anxiety Inventory (STAI) (Spielberger et al., 1983 ), respectively.

**Supplementary Information 4**

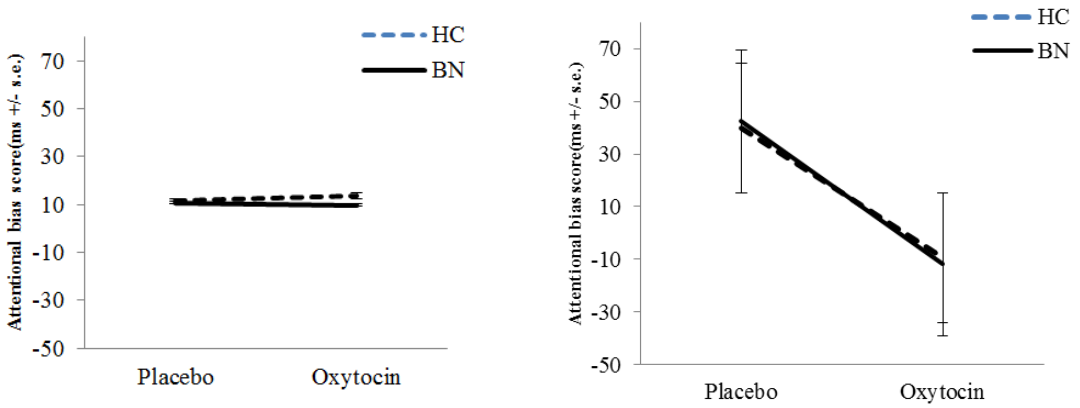
**Trial structure and experimental conditions of the visual probe detection task**

Our target stimuli consisted of 60 images of adults showing 15 happy or 15 angry expressions where each adult had a corresponding picture showing a neutral expression (15 non-target stimuli). The target stimuli were paired with matched non-target stimuli. The task consisted of eight practice trials followed by 160 experimental trials.

As the two images disappear from the screen in a trial, one of the two probes (':' or '‥') appear at the centre of one of the two pictures that used to be there. The participants were then required to press one of two buttons on a keyboard (marked with white stickers) corresponding to the probe (Q for ':' and Z for '‥'). When a response was made, the probe disappeared and the next trial started. The participants were advised to identify the probe as quickly and accurately as possible. The target stimuli positions and the probe positions were balanced across trials, so each appeared in either location (right or left; probe behind the target or non-target) with equal frequency, following the paradigm of Mogg and Bradley (1998). Attention was measured as the time taken to correctly respond to the probe. The participant was assumed to more readily respond to the probe if her attention was already allocated to the place where the probe appears. A quicker response occurred when the probes appeared behind the target stimuli as opposed to when they appeared behind non-target stimuli. This was interpreted as vigilance for a threat. The dot-probe task was presented on the E-Prime software version 2 (Psychology Software Tools, Inc., Pittsburgh, PA, USA).

We followed a standard analytical procedure for the visual probe task (Bradley et al., 1999). Only RTs from trials in which probes were correctly identified were included in the analysis. The correct response rates were 99.9% for the BN group and 99.7% for the HC group. Mean RTs were calculated for each participant, and the outlier trials were removed by excluding detection latencies beyond two standard deviations from their mean (i.e., from each individual's mean RTs across all stimuli).

**Supplementary Information 5**




Happy expression Angry expression

Fig S1. Attentional bias scores for the angry/happy faces under oxytocin/placebo conditions in patients with BN and the healthy women. There were no significant effects from the Drug x Emotion x Group interaction [F(1,228.082)=0.002, p=0.965] or Emotion [F(1,228.082)=0.136, p=0.712] on the AB scores. However, the model revealed significant effects from the Drug x Emotion interactions [F(1,228.082)=6.413, p=0.012] and Drug [F(1,228.082)=6.118, p=0.014], with oxytocin reducing the AB towards angry face in both the patients with BN and the HC participants. A simple effect test showed that the AB to angry faces was attenuated by oxytocin [F(1,120.632)=10.217, p=0.002]. Whereas, the AB to happy faces was not affected by oxytocin [F(1,118.034)=0.002, p=0.962].

*HC = healthy comparisons, BN = patients with bulimia nervosa

**Supplementary Information 6**

**Exploratory analyses**

We additionally explored whether oxytocin induced changes in AB scores correlated with the difficulties regarding emotional regulation. AB delta scores were calculated by subtracting the AB scores in the oxytocin session from the AB scores in the placebo session. Thus, positive delta scores indicated greater AB toward stimuli in placebo conditions while negative delta scores indicated greater AB towards stimuli in oxytocin conditions. Consequently, correlation analyses were conducted to investigate the significant correlation between the delta and psychometric variables.

In the exploratory analysis, AB to angry faces were negatively correlated with EDE-Q in patients with BN (global: r = -0.48, p = 0.006; restraint: r = -0.42, p = 0.017; eating concern: r = -0.45, p = 0.010; shape concern: r = -0.36, p = 0.044; weight concern: r = -0.38, p = 0.034), but not in the HC group (all p-values for global and 4 subscales : p>0.1) for placebo conditions. In HC, AB correlated only with the anger trait (r=0.37, p=0.034) and anger expression (r=0.45, p=0.009) in STAXI.

In the correlation analyses between the AB delta scores and difficulties with emotional regulation, there is a negative correlation of the AB delta scores with anger expression in STAXI subscales (r = -0.508, p = 0.004) and a positive correlation with difficulties engaging in goal-directed behaviour (DERS_goals) (r = 0.408, p = 0.023) in patients with BN. In HC, the AB delta correlated only with anger-expression (r = 0.46, p = 0.007). Table S1 shows the results of correlations between AB and psychometric variables in BN and HC groups.

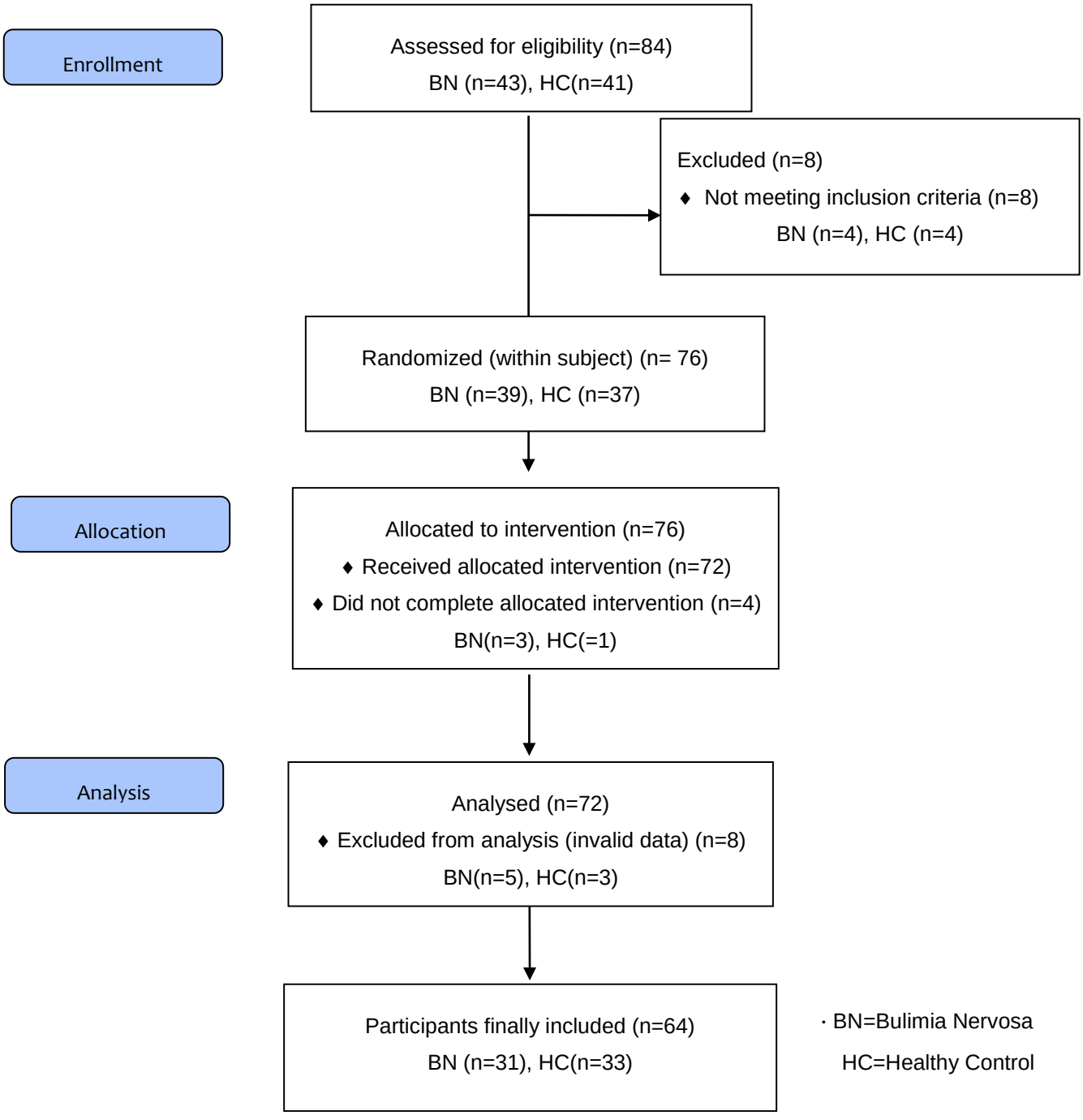
**Supplementary Information 7 – Table S1.** Correlations between the attentional bias scores to angry faces under oxytocin or placebo conditions, as well as psychological variables in patients with bulimia nervosa (n=31) and healthy women (n=33)

| | AB | | | | | | AB delta | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Total (n=64) | | BN (n=31) | | HC (n=33) | | Total (n=64) | | BN (n=31) | | HC (n=33) | |
| | *r* | *p* | *r* | *p* | *r* | *p* | *r* | *p* | *r* | *p* | *r* | *p* |
| EDE-Q | | | | | | | | | | | | |
| Restraint | -0.18 | 0.150 | -0.42* | 0.017 | 0.14 | 0.438 | 0.07 | 0.576 | -0.26 | 0.145 | 0.11 | 0.540 |
| Eating Concern | -0.25* | 0.042 | -0.45* | 0.010 | -0.28 | 0.118 | -0.04 | 0.770 | -0.23 | 0.212 | -0.27 | 0.134 |
| Shape Concern | -0.18 | 0.161 | -0.36* | 0.044 | -0.08 | 0.621 | 0.09 | 0.523 | -0.08 | 0.657 | -0.12 | 0.499 |
| Weight Concern | -0.14 | 0.271 | -0.38* | 0.034 | 0.03 | 0.852 | 0.15 | 0.264 | -0.07 | 0.690 | -0.02 | 0.879 |
| Global | -0.21 | 0.089 | -0.48** | 0.006 | -0.04 | 0.825 | 0.07 | 0.576 | -0.20 | 0.276 | -0.08 | 0.649 |
| BDI | -0.05 | 0.666 | -0.16 | 0.367 | 0.04 | 0.829 | 0.08 | 0.530 | -0.04 | 0.815 | -0.14 | 0.423 |
| STAI | | | | | | | | | | | | |
| State | -0.08 | 0.528 | -0.27 | 0.139 | 0.07 | 0.679 | 0.14 | 0.305 | -0.18 | 0.329 | 0.08 | 0.651 |
| Trait | -0.01 | 0.896 | -0.14 | 0.431 | 0.06 | 0.733 | 0.13 | 0.330 | 0.02 | 0.876 | 0.01 | 0.929 |
| STAXI | | | | | | | | | | | | |
| Anger_State | -0.08 | 0.525 | -0.13 | 0.456 | -0.01 | 0.932 | 0.08 | 0.547 | -0.10 | 0.573 | -0.19 | 0.285 |
| Anger_Trait | 0.24 | 0.052 | 0.13 | 0.472 | 0.37* | 0.034 | 0.05 | 0.706 | 0.18 | 0.318 | 0.23 | 0.187 |
| Anger_Supression | -0.12 | 0.343 | -0.18 | 0.314 | -0.06 | 0.713 | 0.05 | 0.727 | -0.01 | 0.939 | -0.11 | 0.526 |
| Anger_Expression | 0.26* | 0.033 | 0.09 | 0.603 | 0.45** | 0.009 | 0.23 | 0.095 | 0.22 | 0.216 | 0.46** | 0.007 |
| Anger_Control | -0.28* | 0.023 | -0.34 | 0.058 | -0.22 | 0.208 | -0.20 | 0.138 | -0.51** | 0.004 | -0.22 | 0.203 |
| DERS | | | 0.15 | 0.392 | 0.02 | 0.887 | | | 0.21 | 0.250 | 0.00 | 0.972 |
| Non-acceptance | 0.01 | 0.888 | 0.08 | 0.655 | -0.05 | 0.756 | 0.20 | 0.138 | 0.07 | 0.698 | -0.06 | 0.727 |
| Goals | 0.07 | 0.555 | 0.14 | 0.428 | -0.02 | 0.892 | 0.21 | 0.133 | 0.40* | 0.023 | -0.03 | 0.873 |
| Impulsivity | -0.00 | 0.985 | 0.03 | 0.835 | -0.05 | 0.780 | 0.06 | 0.640 | 0.17 | 0.365 | -0.16 | 0.335 |
| Awareness | 0.13 | 0.281 | 0.33 | 0.069 | -0.07 | 0.689 | -0.13 | 0.359 | 0.13 | 0.469 | -0.09 | 0.618 |
| Strategies | 0.00 | 0.978 | -0.00 | 0.988 | -0.02 | 0.907 | 0.13 | 0.330 | 0.05 | 0.786 | 0.05 | 0.767 |
| Clarity | 0.16 | 0.199 | 0.06 | 0.737 | 0.33 | 0.067 | -0.05 | 0.697 | 0.08 | 0.647 | 0.15 | 0.391 |

AB = Attentional bias, AB delta (;Attentional bias delta) = AB scores of the placebo session - AB scores of the oxytocin session, BN = bulimia nervosa, HC = healthy comparison, EDE-Q = Eating Disorder Examination Questionnaire, BDI = Beck Depression Inventory; STAI-State = Spielberger State and Trait Anxiety Inventory State Score, STAI-Trait = Spielberger State and Trait Anxiety Inventory Trait score, STAXI = State and the Trait Anger Expression Inventory, DERS = Difficulties in Emotion Regulation Scale, Non-acceptance = non-acceptance of emotional responses, Goal = difficulties engaging in goal-directed behaviour, Impulse = impulse control difficulties, Awareness = lack of emotional awareness, Strategies = limited access to emotion regulation strategies, Clarity = lack of emotional clarity, *r* = Pearson's correlation coefficient. *p<0.05, ** p<0.01

**Supplementary Information 8**

**CONSORT Flow Diagram**



**Supplementary Information 9**

**CONSORT checklist of information to include when reporting a randomised trial**

| Section/Topic | Item No | Checklist item | Reported on page No |
|---|---|---|---|
| **Title and abstract** | | | |
| | 1a | Identification as a randomised trial in the title | 2 |
| | 1b | Structured summary of trial design, methods, results, and conclusions | 2 |
| **Introduction** | | | |
| Background and objectives | 2a | Scientific background and explanation of rationale | 3 |
| | 2b | Specific objectives or hypotheses | 3 |
| **Methods** | | | |
| Trial design | 3a | Description of trial design (such as parallel, factorial) including allocation ratio | 5 |
| | 3b | Important changes to methods after trial commencement (such as eligibility criteria), with reasons | N/A |
| Participants | 4a | Eligibility criteria for participants | 3-4 |
| | 4b | Settings and locations where the data were collected | 3 |
| Interventions | 5 | The interventions for each group with sufficient details to allow replication, including how and when they were actually administered | 5 |
| Outcomes | 6a | Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed | 5-6 |
| | 6b | Any changes to trial outcomes after the trial commenced, with reasons | N/A |
| Sample size | 7a | How sample size was determined | 4 |
| | 7b | When applicable, explanation of any interim analyses and stopping guidelines | N/A |
| Randomisation: | | | |
| Sequence generation | 8a | Method used to generate the random allocation sequence | 5 |
| | 8b | Type of randomisation; details of any restriction (such as blocking and block size) | N/A |
| Allocation concealment | 9 | Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned | N/A |

| | | | |
|---|---|---|---|
| mechanism | | | |
| Implementation | 10 | Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions | 5 |
| Blinding | 11a | If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how | 5 |
| | 11b | If relevant, description of the similarity of interventions | 5 |
| Statistical methods | 12a | Statistical methods used to compare groups for primary and secondary outcomes | 6 |
| | 12b | Methods for additional analyses, such as subgroup analyses and adjusted analyses | N/A |
| **Results** | | | |
| Participant flow (a diagram is strongly recommended) | 13a | For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome | 7 |
| | 13b | For each group, losses and exclusions after randomisation, together with reasons | 6 |
| Recruitment | 14a | Dates defining the periods of recruitment and follow-up | N/A |
| | 14b | Why the trial ended or was stopped | 5 |
| Baseline data | 15 | A table showing baseline demographic and clinical characteristics for each group | Table1 |
| Numbers analysed | 16 | For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups | Table 1,2 |
| Outcomes and estimation | 17a | For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval) | Table 1,2 |
| | 17b | For binary outcomes, presentation of both absolute and relative effect sizes is recommended | N/A |
| Ancillary analyses | 18 | Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory | N/A |
| Harms | 19 | All important harms or unintended effects in each group (for specific guidance see CONSORT for harms) | N/A |
| **Discussion** | | | |
| Limitations | 20 | Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses | 8 |
| Generalisability | 21 | Generalisability (external validity, applicability) of the trial findings | 8 |
| Interpretation | 22 | Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence | 8 |
| **Other information** | | | |

| | | | |
|---|---|---|---|
| Registration | 23 | Registration number and name of trial registry | 4 |
| Protocol | 24 | Where the full trial protocol can be accessed, if available | 4 |
| Funding | 25 | Sources of funding and other support (such as supply of drugs), role of funders | 9 |

**Supplementary references**

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